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Therapeutic Class Review
Erythropoietin Agents

Overview/Summary

Erythropoietin is a naturally occurring glycoprotein hormone that stimulates the production and maturation of erythrocytes in the bone marrow.[1] Erythrocytes, or red blood cells, are responsible for transporting oxygen from the lungs to the peripheral tissues. Erythropoietin is primarily produced and released into the bloodstream by the kidneys. Renal production of erythropoietin is stimulated when the renal oxygen sensor is triggered by hypoxia or low tissue oxygen.[2-3]

Currently, there are two types of erythropoiesis-stimulating agents (ESAs) available in the United States (US): epoetin alfa (erythropoietin) and darbepoetin alfa (a long-acting form of erythropoietin). Another product, epoetin beta, which is pharmacologically and clinically similar to epoetin alfa, is commercially available in Europe.[4] These agents are manufactured via recombinant deoxyribonucleic acid technology in Chinese hamster ovary cells and have similar biological effects as endogenous erythropoietin.[5] Darbepoetin alfa differs from epoetin alfa in that it is genetically modified to contain two additional carbohydrate chains.[6] Although darbepoetin alfa has identical pharmacological actions, the additional carbohydrate chains prolong the half-life by two- to three-fold compared to the epoetin alfa products.[5]

Epogen® and Procrit® are both trade names of epoetin alfa products available in the US while Aranesp® is the trade name of darbepoetin alfa. Due to the prolonged half-life, darbepoetin alfa is dosed less frequently than the epoetin alfa products. For the treatment of anemia of chronic renal failure, epoetin alfa is recommended to be administered three times a week while darbepoetin alfa is recommended to be administered once weekly. Also, for the treatment of anemia of cancer patients receiving chemotherapy, it is recommended that epoetin alfa be dosed three times weekly or once weekly and darbepoetin alfa be dosed once weekly or once every 3 weeks. Both epoetin alfa and darbepoetin alfa are Food and Drug Administration (FDA) approved for the treatment of anemia due to chronic renal failure and chemotherapy. Additionally, the epoetin alfa products are also FDA approved for treatment of anemia related to therapy with zidovudine in human immunodeficiency virus-infected patients as well as anemic patients who are at high risk for perioperative blood loss from elective, noncardiac, nonvascular surgery to reduce the need for allogeneic blood transfusions. All agents are contraindicated in patients who have uncontrolled hypertension and, while darbepoetin alfa states it is contraindicated in patients with a known hypersensitivity to the active substance or any of the excipients, the epoetin alfa products more specifically state a contraindication in those patients with a known hypersensitivity to mammalian cell-derived products. In addition, the epoetin alfa products list a contraindication to those patients with a known hypersensitivity to albumin (human) because they contain albumin. Darbepoetin alfa comes in two formulations, an albumin solution and a polysorbate solution, which does not contain albumin. Due to the erythropoietin products containing albumin, there is a theoretical risk of transmitting viral diseases and Creutzfeldt-Jakob disease to patients who receive them, although no cases of transmission of either have been identified with albumin.[7-9]

The FDA, Amgen Inc, and Ortho Biotech have issued several "Dear Health Care Professional" letters to address the safety data that arose from clinical studies with the ESA agents. The initial letters sent on March 12, 2007 and November 8, 2007 reviewed changes and clarifications to the Boxed Warnings regarding increased mortality, serious cardiovascular and thromboembolic events and tumor progression with the ESA agents. The letters discussed the increase risk of death in renal failure patients and patients

with cancer, as well as time to tumor progression in cancer patients associated with higher target hemoglobin levels (≥12.0 g/dL) when using ESAs. Additional statements added to the Boxed Warnings noting to use ESAs only for treatment of anemia due to concomitant myelosuppressive chemotherapy and to discontinue ESA treatment following completion of a chemotherapy course.[10-11] A "Dear Health Care Professional" letter was issued on March 7, 2008 to alert health care professionals about revisions to the Boxed Warnings and to include the results of two additional clinical trials demonstrating a shortened survival and/or time to tumor progression in patients with breast cancer, non-small cell lung, head and neck, lymphoid, and cervical cancers when dosed to a target hemoglobin of ≥12.0 g/dL.[12] The most recent "Dear Health Care Professional" letter was issued August 7, 2008 addressing the strengthened oncology and safety information for the ESAs. The product labeling updates included clarification of FDA-approved indications as well as revised dosing instructions to state that ESAs should not be initiated in cancer patients with a hemoglobin ≥10.0 g/dL and that ESAs are not indicated for patients receiving myelosuppressive therapy when the anticipated outcome is curative. In addition, the patient package insert was replaced by two new documents: a Medication Guide and Patient Instructions for Use, which provides important safety information necessary for the safe and effective use of these agents.[13] Please see specific Boxed Warnings detailed later in this review.

The erythropoietin products are generally used for the treatment of anemia due to chronic kidney disease. According to the National Kidney Foundation (NKF), anemia is defined as a deficiency in circulating red blood cells and should be diagnosed when hemoglobin concentrations reach <13.5 g/dL in adult males, and <12.0 g/dL in adult females.[14] Anemia is a common manifestation of chronic kidney disease, and is thought to be due to the decrease in functioning renal mass leading to a decrease in erythropoietin production by the kidney.[15] Anemia may decrease a patient's quality of life by causing fatigue, reduced exercise capacity, decreased cognition, and impaired immunity. Also, left ventricular hypertrophy and maladaptive cardiomyopathy may be a result from anemia increasing the workload on the heart and increasing the risk of death from heart failure or ischemic heart disease.[16] Based on the recommendations from the Kidney Disease Outcome Quality Initiative (K/DOQI) Clinical Practice Guidelines and Clinical Practice Recommendations for Anemia in Chronic Kidney Disease, the hemoglobin level at which ESA therapy should be initiated as well as target hemoglobin levels during therapy should be based on the individual patient, potential benefits (including improvement in quality of life and avoidance of transfusion) and potential harms of therapy (including the risk of life threatening adverse events). Generally speaking, it is recommended that patients with chronic kidney disease, both dialysis and nondialysis, receiving ESA therapy have a hemoglobin target range of 11.0 to 12.0 g/dL and should not be greater than 13.0 g/dL. This recommendation is based on clinical trials demonstrating that patients with hemoglobin concentrations ≥13.0 g/dL do not have improvements in survival, hospitalization, or left ventricular hypertrophy and may actually be more prone to excessive adverse cardiovascular events compared to individuals with lower target hemoglobin concentrations. The guidelines state that the available ESAs are each effective in achieving and maintaining target hemoglobin levels and preference of one agent over another is not provided. More information regarding the use of ESAs and hemoglobin targets is expected to be provided by currently ongoing and future clinical trials in patients with chronic kidney disease.[17-18]

Medications

Table 1. Medications Included Within Class Review

Generic Name (Trade name)	Medication Class	Generic Availability
Darbepoetin alfa (Aranesp®)	Erythropoietin Agents	-
Epoetin alfa (Epogen®, Procrit®)	Erythropoietin Agents	-

Indications

Table 2. Food and Drug Administration Approved Indications[7-9]

Indication	Darbepoetin alfa	Epoetin alfa
Treatment of anemia associated with chronic renal failure, including patients on dialysis and patients not on dialysis	✔	✔ *
Treatment of anemia due to the effect of concomitantly administered chemotherapy based on studies that have shown a reduction in the need for red blood cell transfusions in patients with metastatic, nonmyeloid malignancies	✔	✔ †
Treatment of anemia related to therapy with zidovudine in human immunodeficiency virus-infected patients; to elevate or maintain the red blood cell level (as manifested by hematocrit or hemoglobin determinations) and to decrease the need for transfusions in these patients		✔ ‡
Treatment of anemic patients (hemoglobin of more than 10.0 to less than or equal to 13.0 g/dL) who are at high risk for perioperative blood loss from elective, noncardiac, nonvascular surgery to reduce the need for allogeneic blood transfusions		✔

*To elevate or maintain the red blood cell level (as manifested by hematocrit or hemoglobin determinations) and to decrease the need for transfusions in these patients.
†In patients receiving chemotherapy for a minimum of 2 months.
‡Not indicated for the treatment of anemia in human immunodeficiency virus-infected patients because of other factors.

Although not Food and Drug Administration approved, darbepoetin alfa has been used in the treatment of anemia associated with malignancy and epoetin alfa in the treatment of uremic pruritus. Epoetin alfa has additionally been used off-label for the following conditions: anemia associated with chronic disease, anemia associated with critically ill patients, congestive heart failure, rheumatoid arthritis, postpartum anemia, sickle cell disease, thalassemia, multiple myeloma, radiation treatment, epidermolysis bullosa, porphyria, athletic enhancement, sexual dysfunction and transfusional iron overload.[19]

Pharmacokinetics

Table 3. Pharmacokinetics[7-9]

Generic Name	Bioavailability (%)	Absorption (%)	Renal Excretion (%)	Active Metabolites	Serum Half-Life (hours)
Darbepoetin alfa	37; adult 54; children	Not reported	(% not specified)	Not reported	21; intravenously* 74 (24-144); adult (cancer) 46 (12-89); adult (chronic renal failure) 70 (35-139); adult (not on dialysis)
Epoetin alfa	Not reported	Not reported	(% not specified)	Not reported	4-13; intravenously† 40 (16-67); subcutaneously (cancer)

*Chronic renal failure patients.
†Chronic renal failure patients; approximately 20% longer than healthy adults.

Clinical Trials

There are several clinical trials comparing the efficacy of epoetin alfa and darbepoetin alfa for the treatment of anemia due to chronic renal failure or cancer chemotherapy.

Two non-inferiority trials comparing epoetin alfa and darbepoetin alfa in the treatment of anemia of chronic renal failure demonstrated no difference in efficacy between the two agents. Both studies reported no statistically significant differences in the primary endpoint of mean change in hemoglobin levels from baseline. In addition, there were no differences in safety profiles and no antibodies detected to either treatment in both studies.[20-21]

The Agency for Healthcare Research and Quality (AHRQ) performed a meta-analysis on 57 randomized controlled trials, 7 of which directly compared epoetin alfa and darbepoetin alfa in participants diagnosed with malignant disease that were anemic or at risk for anemia from chemotherapy and/or radiotherapy or the underlying malignant disease. Of the endpoints evaluated, the AHRQ found that the evidence did not show any clinically significant differences between epoetin alfa and darbepoetin alfa in hemoglobin response, transfusion reduction, and thromboembolic events. Of the other endpoints evaluated, it was determined that the evidence was not sufficient for conclusions on effects of either epoetin alfa or darbepoetin alfa on quality of life, tumor response and progression, survival or adverse outcomes.[22]

Darbepoetin alfa is not Food and Drug Administration approved for the treatment of anemia in patients with human immunodeficiency virus who are receiving zidovudine therapy or for the reduction of allogeneic blood transfusions in surgery patients. Currently there are no comparative trials between the erythropoiesis-stimulating agents for these two indications.

Table 4. Clinical Trials

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Treatment of Anemia Associated With Chronic Renal Failure, Including Patients on Dialysis and Not on Dialysis				
Locatelli et al[23] Darbepoetin alfa 0.45 µg/kg SC once weekly vs epoetin alfa 50 U/kg SC twice weekly Study drug dose was adjusted by 25% of the starting dose as necessary to achieve a hemoglobin increase of ≥1.0 g/dL from baseline and to maintain hemoglobin concentrations within a range of 11.0 to 13.0 g/dL.	MC, OL, RCT Patients ≥18 years of age diagnosed with CRI not yet receiving dialysis and rHuEPO-naïve 12 weeks before first planned study dose, a hemoglobin <11.0 g/dL, adequate iron stores (serum ferritin ≥100 µg/L), serum Vitamin B_{12} levels and folate levels above the lower limit of the normal range, and a creatinine clearance of <30 mL/min	N=166 24 weeks	Primary: Proportion of patients achieving a hemoglobin response during the 24-week treatment period, (increase in hemoglobin of ≥1.0 g/dL from baseline and a hemoglobin concentration of ≥11.0 g/dL Secondary: Time to achieve a hemoglobin response, hemoglobin concentration over time, dose of study drug at the time of hemoglobin response and at week 24, number of patients receiving red blood cell transfusions and safety	Primary: Ninety three percent (95% CI, 87% to 97%) of patients in the darbepoetin alfa group and 92% (95% CI, 78% to 98%) of patients in the epoetin alfa group achieved a hemoglobin response (*P* value not reported). Secondary: In both groups, the median time to achieve a hemoglobin response was 7 weeks (3 to 25 weeks). The mean hemoglobin concentration after 4 weeks of therapy was 1.38 g/dL (95% CI, 1.21 to 1.55 g/dL) in the darbepoetin alfa group and 1.40 g/dL (95% CI, 1.07 to 1.72 g/dL) in the epoetin alfa group (*P* value not reported). Mean changes in hemoglobin was similar between the two groups up to 24 weeks (*P* value not reported). At the time of hemoglobin response, the median weekly weight-adjusted dose of darbepoetin alfa was 0.46 µg/kg (0.3 to 2.3 µg/kg), and the corresponding dose of epoetin alfa was 100 U/kg (range of 75 to 175 U/kg). Both doses were nearly identical to those at the beginning of the study. At week 24, median study drug doses had decreased to 0.34 µg/kg (range of 0.00 to 1.30 µg/kg) in patients receiving darbepoetin alfa and to 56.9 U/kg (range of 19.0 to 250.0 U/kg) in patients receiving epoetin alfa (*P* values not reported). Three patients in the darbepoetin alfa group and two patients in the epoetin alfa group required red blood cell transfusions (*P* value not reported). Safety profiles were similar between the 2 groups. Adverse events were reported in 107 patients (83%) in the darbepoetin alfa group and in 24 (65%) patients in the epoetin alfa group and most were mild to moderate in nature (*P* value not reported). The most commonly reported side effects in darbepoetin alfa and epoetin alfa groups were hypertension (32% and 22%, respectively) and peripheral edema (13% and 11%, respectively) (*P* values

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				not reported). There were 6 reported deaths in the study, 4% in the darbepoetin alfa group and 3% in the epoetin alfa group (*P* value not reported).
Nissenson et al[20] Darbepoetin alfa IV once weekly (initial dose was based on their total weekly dose of epoetin alfa at the time of randomization (200 U of epoetin alfa = 1 µg of darbepoetin alfa) vs epoetin alfa IV TIW After a 4-week screening and baseline period, patients were randomized to continue epoetin alfa IV TIW or change to darbepoetin alfa IV once weekly (plus placebo two times weekly). Study drug were adjusted to maintain hemoglobin concentrations within -1 to +1.5 g/dL) of their baseline values and within a range of 9.0 to 13.0 g/dL.	DB, MC, NI, RCT Patients ≥18 years with CKD, clinically stable on HD for at ≥12 weeks, stable on IV epoetin alfa therapy TIW for ≥8 weeks, a mean baseline hemoglobin concentration of 9.5 to 12.5 g/dL and a transferrin saturation of ≥20% or greater	N=504 28 weeks	Primary: Mean change in hemoglobin levels between the baseline and evaluation periods Secondary: Percentage of hemoglobin values within the target range (-1.0 to +1.5 g/dL of baseline and 9.0 to 13.0 g/dL), hemoglobin concentrations necessitating a dose change, within-patient variance in hemoglobin levels, dose of study drug and safety	Primary: The mean changes in hemoglobin levels from baseline to the evaluation period were similar between the darbepoetin alfa (0.16 to 0.09 g/dL) and epoetin alfa (0.00 to 0.06 g/dL) groups, with a difference of 0.16 g/dL (95% CI, -0.06 to 0.38 g/dL; *P* value not reported). Secondary: The 95% CI of the ratio between darbepoetin alfa and epoetin alfa included 1, indicating no statistically significant difference between treatments in each of the secondary endpoints (actual values and *P* values not reported). In the darbepoetin alfa group, 69% of patients had a dose change during the titration period, and 44% changed dose during the evaluation period. In epoetin alfa-treated patients, 73% and 49% had dose changes during the titration and evaluation periods, respectively (*P* values not reported). At least 1 adverse event was reported in 93% of patients in the darbepoetin alfa group and 99% in the epoetin alfa group. The most frequently reported adverse events included nausea (29%, darbepoetin alfa; 27%, epoetin alfa), upper respiratory infection (27%, both groups) and hypertension (28%, darbepoetin alfa; 24%, epoetin alfa) (*P* values not reported). Nine patients (5%) in the darbepoetin alfa group and 23 (7%) in the epoetin alfa group died during the study or within 30 days of the last dose of study drug (*P* value not reported). Deaths were reported by the study investigators as unrelated to study drug.
Vanrenterghem et al[21] Darbepoetin alfa (initial dose was based on their total	MC, OL, RCT Patients ≥18 years with CRF,	N=522 52 weeks	Primary: The mean change in hemoglobin between the	Primary: The mean change in hemoglobin between the baseline and evaluation period was 0.05 g/dL (SD 0.80) in the darbepoetin alfa group and rHuEPO (0.00 g/dL; SD 0.87) for a difference of 0.05 g/dL (95% CI, -0.14 to 0.24

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weekly dose of epoetin alfa at the time of randomization [200 U of epoetin alfa = 1 µg of darbepoetin alfa]) vs rHuEPO After a 4-week screening and baseline period, patients were randomized to continue epoetin alfa at current dose or change to darbepoetin alfa using the same route but at a reduced frequency (i.e. weekly or every other week). Study drug were adjusted to maintain hemoglobin concentrations within -1 to +1.5 g/dL) of their baseline values and within a range of 9.0 to 13.0 g/dL.	clinically stable on HD or PD for ≥6 months, stable on rHeEPO IV therapy given one, two or three times weekly for ≥3 months, a mean baseline hemoglobin of 9.5 to 12.5 g/dL and a serum ferritin of >100 µg/L		baseline and evaluation period Secondary: Proportion of patients necessitating a dose change, within-subject variance of hemoglobin, proportion of patients in the target (-1.0 to +1.5 g/dL of baseline and 9.0 to 13.0 g/dL) and therapeutic (9.0 to 13.0 g/dL) ranges and safety	g/dL; *P* values not reported). Secondary: The ratios (95% CI) between darbepoetin alfa and rHuEPO for each of the secondary endpoints were as follows: proportion of patients necessitating a dose change, within-subject variance of hemoglobin: 0.794 (0.476 to 1.325), proportion of patients in the target ranges: 1.030 (0.855 to 1.242), and therapeutic ranges: 1.036 (0.993 to 1.081) (*P* values not reported). The 95% CI included 1.0 in all secondary endpoints demonstrating no significant differences between the treatment groups. At least 1 adverse event was reported in 96% of patients in the darbepoetin alfa group and 95% in the rHuEPO group. The three most commonly reported adverse events were hypotension (39% darbepoetin alfa, 38% rHuEPO), myalgia (34% darbepoetin alfa, 36% rHuEPO) and hypertension (30% darbepoetin alfa, 28% rHuEPO) and those with the largest reported rates between the groups were pruritis (14% darbepoetin alfa, 5% rHuEPO) and back pain (10% darbepoetin alfa, 16% rHuEPO) (*P* values not reported). There were 52 deaths during the study, 12% of patients (41/346) in the darbepoetin alfa treatment group compared with 6% (11/173; 6%) (*P*=0.062). All deaths were reported by the study investigators as unrelated to study drug.
Treatment of Anemia Due to the Effect of Concomitantly Administered Chemotherapy Based on Studies That Have Shown a Reduction in the Need for Red Blood Cell Transfusions in Patients with Metastatic, Nonmyeloid Malignancies				
Bohlius et al[22] Darbepoetin alfa (no minimal dose was required) or epoetin alfa SC/IV ≥300 U/kg body weight per week	MA of 57 RCT Participants diagnosed with malignant disease, using clinical and histological/ cytological criteria,	N=9,353 >20 weeks	Primary: Hematological response, patients receiving red blood cell transfusions, number of red blood cell units transfused per	Primary: Hematological response occurred in 1,364 of 2,486 participants in the epoetin alfa/darbepoetin alfa groups compared to 286 of 1,821 participants in the control groups (RR, 3.43; 95% CI, 3.07 to 3.84; *P* value not reported). The relative risk of red blood cell transfusions was significantly reduced in the epoetin alfa/darbepoetin alfa groups compared to the control group (RR, 0.64; 95% CI, 0.60 to 0.68; *P* value not reported).

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for at least four weeks vs placebo/no treatment	regardless of type or stage of the disease or previous therapy, anemic or at risk for anemia from chemotherapy and/or radiotherapy or the underlying malignant disease		patient, and overall survival Secondary: Tumor response (complete response), changes in quality of life including cancer-related fatigue, and adverse events	On average, participants in the epoetin alfa/darbepoetin alfa group received one unit of blood less than the control group (WMD, -1.05; 95% CI, -1.32 to -0.78; *P* value not reported. Overall survival demonstrated a hazard ratio of 1.08 (95% CI, 0.99 to 1.18) in favor of placebo/no treatment but the effect is uncertain (*P* value not reported). Secondary: The overall estimate of tumor response showed a relative risk of 1.12 (95% CI, 1.01 to 1.23) in favor of erythropoietin but the effect is uncertain (*P* value not reported). The results show an overall positive effect on quality of life from epoetin alfa, which seems unlikely to be due to chance. The size of this effect is impossible to speculate on using the method of analysis employed. What was noted was that for participants with baseline hemoglobin below 12.0 g/dL, hematological response was observed more often in participants receiving epoetin alfa/darbepoetin alfa (RR, 3.43; 95% CI, 3.07 to 3.84; *P* value not reported. For adverse events, the relative risk for thromboembolic complications was increased in patients receiving epoetin alfa/darbepoetin alfa compared to controls (RR, 1.67, 95% CI, 1.35 to 2.06). The relative risk to develop hypertension for erythropoietin treated participants was increased by 24% (RR, 1.24; 95% CI, 1.00 to 1.54). The relative risk of developing thrombocytopenia was not increased in the erythropoietin-treated participants (RR, 1.13; 95% CI, 0.08 to 1.60). Overall 21 events of skin rash, irritations or pruritus in the erythropoietin group (N=395) and 11 cases in the control group (N=280) were reported resulting in a relative risk of 1.17 (95% CI, 0.63 to 2.18). There was no evidence for significant differences in seizures between the groups compared (RR, 1.19, 95% CI, 0.33 to 4.35; *P* values not reported.

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Seidenfeld et al[4] Darbepoetin alfa (no minimal dose was required) vs epoetin alfa SC/IV ≥300 U/kg body weight per week for at least four weeks or darbepoetin alfa or epoetin alfa vs observation (alone or with placebo)	MA of 59 RCT Patients diagnosed with malignant disease and undergoing treatment with chemotherapy or radiotherapy	N=6,531 ≤16 weeks	Primary: Hematologic response, rates of transfusions, thromboembolic events Secondary: Quality of life, tumor response and progression, survival and adverse outcomes	Primary: Although a meta-analysis on hematological response was not performed due to differences in the definition of response, five of six trials comparing darbepoetin alfa to epoetin alfa showed no statistically significant difference between these drugs. For rates of transfusion, trials comparing darbepoetin alfa to epoetin alfa showed no statistically significant difference between these drugs (RR, 1.10; 95% CI, 0.93 to 1.29; *P* value not reported. For thromboembolic events, trials comparing darbepoetin alfa to epoetin alfa showed no statistically significant difference between these drugs (RR, 0.86; 95% CI, 0.61 to 1.21; *P* value not reported. Secondary: The evidence is not sufficient for conclusions on effects of either epoetin alfa or darbepoetin alfa on quality of life, tumor response and progression, survival or adverse outcomes other than thromboembolic events (*P* values not reported). Trials did not completely or consistently report quality of life results. Overall, quality of life measures tended to favor treatment with epoetin alfa or darbepoetin alfa. However, the degree of change varied widely across studies and not all positive changes were statistically significant (*P* values not reported). The limited evidence available (five studies, N=688) does not suggest that erythropoietic stimulants improve solid tumor response to a concurrent course of cancer therapy, (*P* values not reported). Of 40 (N=8,249) RCTs reporting on survival, only seven (N=2,188) were actually designed to assess effects on survival (progression free or overall). No studies designed to test survival used epoetin alfa or darbepoetin alfa as currently recommended; rather, all seven trials sought to maintain hemoglobin levels >12.0 g/dL. Analysis of mortality in all 40 trials showed

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				no overall benefit of darbepoetin alfa or epoetin alfa on survival (*P* value not reported). For other adverse events, reporting is incomplete, representing less than one-third of patients. Studies did not use consistent definitions of events and severity. Overall, adverse events were more frequent with epoetin alfa or darbepoetin alfa than control, but pooled results did not show statistically significant differences.
Glaspy, Vadhan-Raj et al[24] Darbepoetin alfa 200 µg every 2 weeks vs epoetin alfa 40,000 units every week For both treatment arms, a 50% dose escalation was permitted at week 5 if the hemoglobin increase was <1 g/dL. Study drug was withheld if a patient's hemoglobin >13.0 g/dL at any time, and was reinstated at 75% of the previously administered dose after the hemoglobin concentration decreased to ≤12.0 g/dL	MC, OL, RCT Patients ≥18 years with a diagnosis of nonmyeloid malignancy with ≥8 weeks of planned chemotherapy, anemia (hemoglobin ≤11.0 g/dL), adequate renal and liver function and the ability to provide written informed consent	N=1,220 18 weeks	Primary: Incidence of red blood cell transfusion from week 5 to end of treatment period Secondary: Transfusion requirements over the entire treatment period, proportion of patients achieving a hemoglobin ≥11.0 g/dL, those who subsequently maintained hemoglobin concentration in the target range (11.0 to 13.0 g/dL), mean hemoglobin change from baseline, HRQOL and safety	Primary: Twenty-one percent (95% CI, 17% to 24%) of patients in the darbepoetin alfa group received a red blood cell transfusion between week 5 and the end of the treatment period compared to 16% (95% CI, 12% to 19%) of patients in the epoetin alfa group (*P* value not reported). Noninferiority was concluded due to the upper 95% CI limit of the difference between groups (10.8%) being below the prespecified noninferiority margin of 11.5%. Secondary: Twenty-seven percent (95% CI, 24% to 31%) of patients in the darbepoetin alfa group received a red blood cell transfusion over the entire treatment period compared to 22% (95% CI, 19% to 26%) of patients in the epoetin alfa group (*P* value not reported). Noninferiority was concluded due to the upper 95% CI limit of the difference between groups being below the prespecified noninferiority margin of 11.5%. Eighty percent (463 patients) achieved target hemoglobin level of ≥11.0 g/dL in the darbepoetin alfa group compared to 86% (487 patients) in the epoetin alfa group (*P* values not reported). Of these patients, 341 patients (74%) in the darbepoetin alfa group and 389 patients (80%) maintained hemoglobin concentration in the target range (*P* value not reported). In both groups, the mean hemoglobin concentrations improved from approximately 10.2 g/dL at baseline to 11.8 g/dL by the end of the treatment period (*P* value not reported). No differences were observed between the two groups for any of the other

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				HRQOL assessments (fatigue, anemia, emerge, daily activity and overall health) (*P* values not reported). The safety profiles of darbepoetin alfa and epoetin alfa were similar with no differences observed between groups. Cardiovascular/thromboembolic events were reported in 6% of patients the darbepoetin alfa group and 7% of patients in the epoetin alfa group. The death rates 11% the darbepoetin alfa group and 14% in the epoetin alfa group (*P* values not reported).
Case et al[25] Darbepoetin alfa at recommended doses vs epoetin alfa at recommended doses The majority of patients in the darbepoetin alfa arm received dosages of 200 µg every other week (93%) while the others received 100 µg weekly or 300 µg every other week. In the epoetin alfa arm most patients received a dosage of 40,000 Units weekly (86%) with the remainder receiving 60,000 Units weekly	RETRO Patients with a gynecologic malignancy (cervical, ovarian endometrial, or vaginal), receiving chemotherapy with ≥1 agent in a single outpatient setting, chemotherapy induced anemia (hemoglobin <10.0 g/dL), and have received at ≥2 dosages of either darbepoetin alfa or epoetin alfa	N=123 Duration not specified	Primary: Transfusion rates Secondary: Change in hemoglobin after receiving ≥2 dosages of each agent, and dosage/ frequency of administration of each agent	Primary: Twenty-one patients in the in the darbepoetin alfa group received a transfusion compared to 12 patients in the epoetin alfa group (*P*=0.05). Secondary: The mean change in hemoglobin after receiving ≥2 dosages was 2.5 g/dL for the darbepoetin alfa group and 2.3 g/dL for the epoetin alfa group and was not statistically significant (*P* value not reported). Patients in the epoetin alfa did receive an increased number of respective erythropoietic stimulating factor (5.7 darbepoetin alfa and 8.1 epoetin alfa; *P*=0.001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Treatment of Anemia Related to Therapy with Zidovudine in Human Immunodeficiency Virus-Infected Patients; to Elevate or Maintain Red Blood Cell Level and to Decrease Need for Transfusions				
Henry et al[26] RHuEPO 100-200 U/kg IV or SC TIW vs placebo IV or SC TIW Dosing was to continue for 12 weeks or until a hematocrit of ≥38% (without a transfusion in the previous 4 weeks) was achieved. Results were evaluated based on patients' endogenous erythropoietin levels (low:≤500 IU/L or high:>500 IU/L)	MA of 4 DB, MC, RCT Patients 18 to 75 years, a diagnosis of AIDS (based on CDC criteria), a performance status of 0, 1, 2 according to the system of Miller et al[27], a hematocrit of ≤30% and were dependant on transfusions, had at least a 15% decline in hematocrit since the initiation of zidovudine therapy	N=297 Up to 12 weeks	Primary: Changes in hematocrit, transfusion requirements, quality of life and safety Secondary: Not reported	Primary: Patients whose serum endogenous erythropoietin level was ≤500 IU/L and received rHuEPO had significantly greater increases hematocrit from baseline compared to the placebo group (mean change, 4.6 vs 0.5, respectively; *P*=0.0002, mean difference, 3.9; 95% CI, 1.8 to 6.0). Of the patients whose serum endogenous erythropoietin level was >500 IU/L, there were no significant differences in changes in hematocrit levels from baseline between the rHuEPO group and the placebo group (mean change, 3.2 vs 2.2, respectively; *P*>0.2, mean difference, 0.9; 95% CI, -2.1 to 3.9). Patients with low serum endogenous erythropoietin level and received rHuEPO had significantly lower transfusion requirements compared to the placebo group (mean units per patient, 3.19 vs 5.34 units, respectively; *P*=0.003, mean difference, –1.88; 95% CI, –3.18 to –0.58). Of the patients with high serum endogenous erythropoietin levels, there were no significant differences in transfusion requirements between the rHuEPO group and the placebo group (mean units per patient, 9.35 vs 8.83, respectively; *P* value not reported, mean difference, 0.22; 95% CI, –1.28 to 1.72). In the patients with low serum endogenous erythropoietin levels, there were no significant differences in the overall quality of life score between the rHuEPO and placebo groups (mean change, 0.92 vs –5.33, respectively; *P*=0.13). Scores for the patients with high erythropoietin levels were not reported. No important differences in the incidence or severity of adverse experiences (i.e. pyrexia, fatigue, headache, and cough) observed between the rHuEPO and placebo groups (*P* values not reported). Two patients in the placebo group and four in the rHuEPO group died during the study (*P*

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				value not reported). Secondary: Not reported
Treatment of Anemic Patients (Hemoglobin >10.0 to <13.0 g/dL) at High Risk for Perioperative Blood Loss From Elective, Noncardiac, Nonvascular Surgery to Reduce the Need for Allogeneic Blood Transfusions				
Faris et al[28] Group 1: RHuEPO 100 IU/kg/day SC vs Group 2: rHuEPO 300 IU/kg/day SC vs Group 3: placebo SC daily The study medication was administered for 15 consecutive days, beginning 10 days before the operation and extending through to the 4th postoperative day. Patients were also stratified into two groups based on the pre-treatment hemoglobin level and assessed.	DB, MC, RCT Patients ≥18 years scheduled to have a major orthopedic procedure in which transfusion of ≥2 units of whole blood or red blood cells is usually required during or after the procedure, who could not or did not choose to donate autologous blood preoperatively, and, if female, had been postmenopausal for ≥1 year, were sterile, or were using a reliable method of birth control and had had a negative pregnancy	N=200 4 weeks	Primary: Percentage of patients who were transfused and the number of units of blood that each patient received Secondary: Change in erythroid parameters and safety	Primary: Significantly fewer patients in the rHuEPO treatment groups required transfusions compared to those in the placebo group (Group 1: 9 patients (17%), Group 2: 16 patients (25%) and Group 3: 36 patients (54%); $P \leq 0.001$ for both rHuEPO groups compared to placebo). There was no significant difference demonstrated between the two rHuEPO groups (*P* value not reported). The mean number of units transfused for each patient was significantly lower in the rHuEPO groups compared to the placebo group (Group 1: 0.37±0.96, Group 2: 0.58±1.15 and placebo: 1.42±1.67; $P<0.01$ for both rHuEPO groups compared to placebo). There was no significant difference between Groups 1 and 2 ($P>0.05$). In those patients who had a baseline hemoglobin level of 100 to 130 g/L, rHuEPO significantly reduced the proportion who received a red-blood-cell transfusion compared with the proportion in the group that received the placebo (14% [3 patients] in Group 1, 39% [9 patients] in Group 2, and 78% [21 patients] in Group 3; $P \leq 0.009$). For patients who had a baseline hemoglobin level of ≥130 g/L (14% [4 patients] in Group 1, 11% [4 patients] in Group 2, and 36% [14 patients] in Group 3; $P=0.03$). Adverse events were reported in 97% of patients (58 patients) in Group 1, 92 % (65 patients) in Group 2 and 93% (64 patients) in Group 3. Nine percent (6 patients) in Group 3 reported depression, compared with no patients in Group 1 ($P<0.05$), 10% (7 patients) in Group 3 reported chest pain, compared with 1% (1 patient) in Group 2 ($P<0.05$) and 10% (7 patients) in Group 3 reported chest pain compared to 2% (3 patients) in Groups 1 and 2 combined ($P<0.05$). Reports of thrombotic and vascular

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	test immediately before being enrolled in the study			events were not significantly different between the rHuEPO and placebo groups (*P*=0.40).
deAndrade at al[29] Epoetin alfa 100 IU/kg SC daily vs epoetin alfa 300 IU/kg SC daily vs placebo SC daily The study medication was administered for 15 consecutive days, beginning 10 days before the operation and extending through to the 4th postoperative day. Patients were stratified based on their entry hemoglobin level (stratum 1: hemoglobin ≤10.0 g/dL, stratum 2; hemoglobin >10.0 to ≤13.0 g/dL and stratum 3: hemoglobin > 13.0 g/dL).	DB, MC, PC, PG Patients ≥18 years scheduled for elective orthopedic surgery of the hip or knee, in good general health with no clinically significant abnormal lab values, expected to require ≥2 units of blood without having participated in a PAD program, have a hemoglobin level ≤15.0 g/dL, and a serum iron to TIBC ratio ≥15% and a serum ferritin level of ≥50 ng/mL	N=316 6 weeks	Primary: Risk of transfusion Secondary: Mean number of units transfused per patient, hemoglobin, hematocrit and reticulocyte levels	Primary: Overall, 11% of patients treated with epoetin alfa 100 IU/kg, 11% of patients in the epoetin alfa 300 IU/kg and 23% of patients in the placebo group received allogenic red blood cell transfusions (*P* values not reported). Those patients in stratum 2 (hemoglobin: >10.0 to ≤13.0 g/dL) experienced significantly less transfusions (16%) compared to placebo (45%; *P*=0.024). Secondary: Overall, the mean number of units transfused per person was significantly lower in those patients treated with epoetin alfa compared to placebo (*P*=0.0278). Those patients in stratum 2, the mean number of units transfused was 1.140±1.432 in the placebo group compared to 0.420±0.945 (*P*=0.0180) in the epoetin alfa 100 IU/kg group and 0.450±1.207 (*P*=0.0229) in the epoetin alfa 300 IU/kg group. The mean hemoglobin, hematocrit and reticulocyte levels were higher in the epoetin alfa treated patients than in the placebo treated patients through postsurgery day 7 in patients in stratum 2 (*P* values not reported). In stratum 2 during the prestudy to presurgery period, significantly greater increases in mean hemoglobin and reticulocyte counts were noted in the epoetin alfa groups compared to placebo (*P*=0.0001 for both). Epoetin alfa was safe and well tolerated. The incidence of adverse events was similar across treatment groups and across baseline hemoglobin strata. Most commonly reported adverse events were: pyrexia (epoetin alfa 300 IU/kg: 57 patients [51%], epoetin alfa 100 IU/kg: 50 patients [50%], and placebo: 62 patients [60%]), nausea (epoetin alfa 300 IU/kg: 54 patients [48%], epoetin alfa 100 IU/kg: 43 patients [43%], and placebo: 46 patients [45%]), and constipation (epoetin alfa 300 IU/kg: 48 patients [43%], epoetin alfa 100 IU/kg: 42 patients [42%], and placebo: 44 patients [43%]); *P* values not reported.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Christodoulakis et al[30] Epoetin alfa 150 IU/kg SC daily vs epoetin alfa 300 IU/kg SC daily vs control group Patients received treatment beginning 10 days before surgery until the day after surgery.	OL Patients >18 years undergoing elective colorectal surgery for resectable colorectal cancer with a hemoglobin level of >9.0 and <12.0 g/dL	N=223 Duration not specified	Primary: Need for blood transfusions Secondary: Effects on hematocrit, hemoglobin and reticulocyte count	Primary: Patients in the 300 IU/kg epoetin alfa group required significantly fewer transfusion units compared to the control patients, both perioperatively (0.81±1.22 [0–5] vs 1.34±1.59 [0–7], respectively; *P*=0.016) and postoperatively (0.87±1.21 [0–4] vs 1.35±1.58 [0–7], respectively; *P*=0.023). The epoetin alfa 150 IU/kg group was not significantly different from the control group (perioperatively: 1.19±1.46 [0–7] and postoperatively: 1.10±1.42 [0–7]; *P* values not reported). Secondary: Mean hematocrit levels were significantly higher in the 150 IU/kg epoetin alfa group than in the control group at day -1 (*P*=0.031) and at day +15 (*P*=0.030); however, the 300 IU/kg epoetin alfa group obtained significantly higher mean hematocrit levels than the 150 IU/kg group (*P*=0.031 and *P*=0.030, respectively). Significantly greater increase in hemoglobin concentrations were seen with the epoetin alfa groups compared to the control group (*P*<0.004 for both epoetin alfa groups vs control). Reticulocyte and white blood cell counts in both the 150 and 300 IU/kg epoetin alfa groups were significantly lower than in the control group at baseline (day -10; *P*<0.05) but there were no other significant differences in hematological values at any time point (*P* values not reported).
Goldberg et al[31] Epoetin alfa 300 IU/kg SC daily for 10 days prior to surgery, on the day of surgery, and for 4 days postoperatively vs epoetin alfa 600 IU/kg SC	MC, OL, PG, RCT Patients ≥18 years scheduled for major elective orthopedic surgery involving hip or knee replacement, in good general health, not enrolled in a PAD	N=145 Duration not specified	Primary: Mean change in hemoglobin and absolute reticulocyte counts from prestudy to presurgery Secondary: Proportion of patients	Primary: Mean change in hemoglobin from prestudy to presurgery in the epoetin alfa 600 IU/kg group was 1.44±1.03 g/dL compared to 0.73±0.87 g/dL in the epoetin alfa 300 IU/kg group (95% CI, 0.3786 to 1.0326; *P* value not reported). Mean change in absolute reticulocyte counts from prestudy to presurgery in the epoetin alfa 600 IU/kg group was $0.110\pm0.069 \times 10^6$ cells/mm^3 compared to $0.170\pm0.070 \times 10^6$ cells/mm^3 in the epoetin alfa 300 IU/kg group (95% CI, -0.1515 to 0.0326; *P* value not reported).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
once per week for 3 weeks prior to surgery and on the day of surgery	program prior to surgery, provided informed consent, had a hemoglobin level ≥10.0 to ≤13.0 g/dL, a serum iron to TIBC ratio ≥0.20 and a serum ferritin ≥50 ng/mL		transfused, mean change in hemoglobin and reticulocyte counts presurgery to postsurgery day 1, total units transfused per patient, reasons for transfusion and safety	Secondary: The proportion of patients transfused in the epoetin alfa 600 IU/kg group was 16% (11 patients) compared to 20% (14 patients) in the epoetin alfa 300 IU/kg group (95% CI, -16.44 to 8.88; *P* value not reported). Mean change in hemoglobin from presurgery to postsurgery day 1 in the epoetin alfa 600 IU/kg group was -2.94±1.43 g/dL compared to -2.30±1.30 g/dL in the epoetin alfa 300 IU/kg group (95% CI, -1.0393 to -0.2374; *P* value not reported). Mean change in absolute reticulocyte counts from presurgery to postsurgery day 1 was -0.05±0.05x10^6 cells/mm^3 in both the epoetin alfa 600 IU/kg and epoetin alfa 300 IU/kg group (95% CI, -0.0845 to 0.0848; *P* value not reported). The mean number of units of allogenic blood transfused per patient was 0.33±0.87 in the epoetin alfa 600 IU/kg compared to 0.30±0.64 in the epoetin alfa 300 IU/kg group (95% CI, -0.2526 to 0.3277). Anemia (hemoglobin <9.0 g/dL) was the most common reason for transfusion which accounted for 68.8% of all transfusions. At least one adverse event was reported in 70 patients (96%) in the epoetin alfa 600 IU/kg group compared to 71 patients (99%) in the epoetin alfa 300 IU/kg group (*P* value not reported). The most commonly reported adverse events included constipation, pyrexia and nausea. One death was reported in the epoetin alfa 600 IU/kg group although it was reported to be unlikely related to the drug. Four patients (5%) in the epoetin alfa 600 IU/kg group reported thrombotic/vascular events and none were reported in the 300 IU/kg group; deaths were reported to be unrelated to the study drug.
Feagan et al[32] Low-dose group: Epoetin alfa 20,000 U SC weekly	DB, MC, PG, RCT Adult patients undergoing total hip joint	N=201 Duration not specified	Primary: Allogenic transfusion Secondary:	Primary: The percent of patients who received an allogenic transfusion in each of the groups was as follows: 11.4% (5 of 44 patients) in the high-dose epoetin alfa group and 22.8% (18 of 79 patients) in the low-dose epoetin alfa group compared with 44.9% (35 of 78 patients) in the placebo group (*P*=0.001

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs High-dose group: epoetin alfa 40,000 U SC weekly vs placebo SC weekly Therapy was initiated 4 weeks prior to surgery. The total possible dose was 160,000 U in the high-dose group and 80,000 U in the low-dose group. The study drug was withheld if the hemoglobin ≥150 g/L, if systolic blood pressure was ≥200 mm Hg, or the diastolic blood pressure was ≥105 mm Hg	arthroplasty, had a hemoglobin concentration of 98.0 to 137.0 g/L and did not predonate blood		Change in reticulocyte count and hemoglobin concentration, thromboembolic events and adverse events	and *P*=0.003, respectively, for treatments vs placebo). Secondary: Mean reticulocyte counts significantly increased in the high-dose epoetin alfa ($58.8x10^9$ cells/L) compared to the low-dose epoetin alfa group ($37.0x10^9$ cells/L; *P*=0.003) and placebo ($1.8x10^9$ cells/L; *P*<0.001). Mean hemoglobin concentrations increased in the high-dose group (19.5 g/L) and low-dose group (17.2 g/L), whereas little change occurred in the placebo group (1.2 g/L; *P*<0.001. Occurrences of thrombotic events (DVT/PE) occurred in the 2 patients in the high-dose group, 5 patients in the low-dose group and 6 patients in the placebo group (*P* value not reported). The proportion of patients who experienced any serious adverse event was similar in the three study groups: 8.5% in the placebo group, 3.5% in the low-dose epoetin alfa group, and 6.5% in the high-dose epoetin alfa group (*P* value not reported).

Drug regimen abbreviations: IV=intravenous, SC=subcutaneous, TIW=three times weekly
Study abbreviations: DB=double-blind, MA=meta-analysis, MC=multicenter, NI=noninferiority, OL=open-labeled, RCT=randomized controlled trial, RETRO=retrospective
Miscellaneous abbreviations: AIDS=acquired immunodeficiency syndrome, CDC=Centers for Disease Control, CI=confidence interval, CIA=chemotherapy-induced anemia, CKD=chronic kidney disease, CRF=chronic renal failure, CRI=chronic renal insufficiency, DVT=deep vein thrombosis, HD=hemodialysis, HRQOL= health-related quality of life, PAD=preoperative autologous donation, PC=placebo controlled, PD=peritoneal dialysis, PE=pulmonary embolism, PG=parallel group, rHuEPO= recombinant human erythropoietin, RR=relative risk, SD=standard deviation, TIBC=total iron-binding capacity, WMD=weighted mean differences

Special Populations

Table 5. Special Populations[7-9]

Generic Name	Population and Precaution				
	Elderly/ Children	Renal dysfunction	Hepatic dysfunction	Pregnancy Category	Excreted in Breast Milk
Darbepoetin alfa	No specific recommendations for elderly reported. Safety and efficacy in pediatric cancer patients, and chronic renal failure patients less than 1 year of age have not been established.	Patients with chronic renal failure not yet requiring dialysis may require lower maintenance doses. Patient maintenance dose should be individualized.	Not reported	C	Unknown
Epoetin alfa	No specific recommendations for elderly reported. Safety and efficacy in pediatric patients less than 1 month old have not been established.*	Patient maintenance dose should be individualized.	Not reported	C	Unknown

*Benzyl alcohol, found in multidose preserved formulations, has been reported to be associated with an increased incidence of neurological and other complications in premature infants, which are sometimes fatal.[7-9]

Adverse Drug Events

The following table presents the most common (occurring greater than 5%) adverse events reported with erythropoietin agents. A potential for immunogenicity does exist with these agents and has been documented in post marketing reports.[7-9]

Table 6. Adverse Drug Events (%)[7-9]

Adverse Event	Darbepoetin alfa	Epoetin alfa
Cardiovascular		
Angina pectoris/cardiac chest pain	8	-
Cardiac arrhythmias/cardiac arrest	8	-
Chest pain, unspecified	7	7
Congestive heart failure	5	-
Hypertension	20	10-24
Hypotension	20	-
Thrombosis vascular access	6	-
Central Nervous System		
Anxiety	-	5-11
Dizziness	7-14	5-21
Fatigue	9-33	9-25
Fever	7-19	-
Headache	12-15	10-19
Insomnia	-	13-21
Dermatological		
Access hemorrhage	7	-

Adverse Event	Darbepoetin alfa	Epoetin alfa
Access infection	6	-
Clotted access	-	7
Injection site pain/reaction	6	7-29
Pruritus	6	14-22
Rash	7	16
Skin pain	-	4-18
Gastrointestinal		
Abdominal pain	10	-
Constipation	5-18	42-53
Diarrhea	14-22	6-58
Dyspepsia	-	8-11
Nausea	11	11-17
Vomiting	14	8-29
Musculo-skeletal		
Arthralgia	9-13	11
Back pain	7	-
Limb pain	8	-
Muscle spasm	17	-
Myalgia	8	-
Respiratory		
Bronchitis	5	-
Congestion	-	15
Cough	9	18
Dyspnea	10	-
Shortness of breath	-	13-14
Upper respiratory infection	15	11
Other		
Asthenia	5	7-13
Death	6	-
Dehydration	5	-
Edema	21	6-17
Fluid overload	6	-
Infection	24	-
Influenza like symptoms	6	-
Paresthesia	-	11
Peripheral edema	10	-
Pyrexia	-	29-51
Thrombotic events	6.2	3-10
Urinary tract infection	-	3-12

-Event not reported.

Contraindications / Precautions

All of the erythropoietin agents are contraindicated in individuals with uncontrolled hypertension. Additionally darbepoetin alfa is contraindicated in patients with a known hypersensitivity to the active substance or any of the excipients. Epoetin alfa is also contraindicated in patients with a known hypersensitivity to mammalian cell-derived products or albumin (human).[7-9]

All of the erythropoietin agents have been assigned Black Box Warnings, which are outlined below. These warnings highlight an increased mortality, serious cardiovascular and thromboembolic events and increased risk of tumor progression or recurrence with the use of these agents. The manufacturer product packaging was updated in August of 2008 to highlight these risks and indicate which patient populations are at the greatest risk for these potential life threatening adverse events.[7-9]

In addition to the contraindications and Black Box Warnings the erythropoietin agents have also been associated with seizures, pure red cell aplasia and allergic/hypersensitivity reactions. Caution should be used when administering these agents to patients who have experienced these drug-related toxicities while receiving an earlier course of therapy.[7-9]

Black Box Warning for Darbepoetin alfa[7-9,19]

WARNING
Increased mortality, serious cardiovascular and thromboembolic events, and increased risk of tumor progression or recurrence: Renal failure: Patients experienced greater risks for death and serious cardiovascular events when administered erythropoiesis-stimulating agents (ESAs) to target higher versus lower hemoglobin levels (13.5 vs 11.3 g/dL; 14 vs 10 g/dL) in 2 clinical studies. Individualize dosing to achieve and maintain hemoglobin levels within the range of 10 to 12 g/dL. Cancer: • ESAs shortened overall survival and/or increased the risk of tumor progression or recurrence in some clinical studies in patients with breast, non-small cell lung, head and neck, lymphoid, and cervical cancers. • To decrease these risks, as well as the risk of serious cardiovascular and thrombovascular events, use the lowest dose needed to avoid red blood cell transfusion. • Use ESAs only for treatment of anemia due to concomitant myelosuppressive chemotherapy. • ESAs are not indicated for patients receiving myelosuppressive therapy when the anticipated outcome is cure. • Discontinue following the completion of a chemotherapy course.

Black Box Warning for Epoetin alfa[7-9,19]

WARNING
Increased mortality, serious cardiovascular (CV) and thromboembolic events, and increased risk of tumor progression or recurrence: Renal failure: Patients experienced greater risks for death and serious CV events when administered erythropoiesis-stimulating agents (ESAs) to target higher versus lower hemoglobin levels (13.5 vs 11.3 g/dL; 14 vs 10 g/dL) in 2 clinical studies. Individualize dosing to achieve and maintain hemoglobin levels within the range of 10 to 12 g/dL. Cancer: • ESAs shortened overall survival and/or increased the risk of tumor progression or recurrence in some clinical studies in patients with breast, non–small cell lung, head and neck, lymphoid, and cervical cancers. • To decrease these risks, as well as the risk of serious cardio- and thrombovascular events, use the lowest dose needed to avoid red blood cell transfusions. • Use ESAs only for treatment of anemia caused by concomitant myelosuppressive chemotherapy. • ESAs are not indicated for patients receiving myelosuppressive therapy when the anticipated outcome is cure. • Discontinue following the completion of a chemotherapy course. Perisurgery: Epoetin alfa increased the rate of deep venous thromboses in patients not receiving prophylactic anticoagulation. Consider deep venous thrombosis prophylaxis. See also Warnings/Precautions, Indications, and Administration and Dosage for more information.

Drug Interactions

There are no specific drug interactions reported with the use of the erythropoietin agents.[7-9,19]

Dosage and Administration

In order to ensure effective erythropoiesis, evaluate iron stores prior to and during therapy with erythropoietin agents, The majority of patients will eventually require supplemental iron therapy Additionally, after administration of an erythropoietin agent the hemoglobin should be monitored routinely until it has stabilized and the maintenance dose has been established. Once stabilized the hemoglobin should be monitored at regular intervals.[7-9]

Table 7. Dosing and Administration[7-9]

Generic Name	Adult Dose	Pediatric Dose	Availability
Darbepoetin alfa	Treatment of anemia associated with chronic renal failure: Initial, 0.45 µg/kg SC or IV once weekly (0.75 µg/kg SC once every 2 weeks if not on dialysis); maintenance, dose should be individualized to maintain a hemoglobin level of 10.0-12.0 g/dL Treatment of anemia due to the effect of concomitantly administered chemotherapy: Initial, 2.25 µg/kg SC once weekly or 500 µg SC once every 3 weeks; maintenance, dose should be individualized to maintain the lowest hemoglobin level sufficient to avoid red blood cell transfusion	Safety and efficacy in pediatric cancer patients, and chronic renal failure patients less than 1 year of age have not been established.	Single dose vial (polysorbate solution or albumin solution): 25 µg/ mL 40 µg/ mL 60 µg/ mL 100 µg/ mL 150 µg/ 0.75 mL 200 µg/ mL 300 µg/ mL 500 µg/ mL Single dose prefilled syringe (polysorbate solution or albumin solution): 25 µg/ 0.42 mL 40 µg/ 0.4 mL 60 µg/ 0.3 mL 100 µg/ 0.5 mL 150 µg/ 0.3 mL 200 µg/ 0.4 mL 300 µg/ 0.6 mL 500 µg/ mL
Epoetin alfa	Treatment of anemia due to the effect of concomitantly administered chemotherapy: Initial, 150 Units/kg SC TIW or 40,000 Units SC weekly; maintenance, dose should be individualized to maintain the lowest hemoglobin level sufficient to avoid red blood cell transfusion Treatment of anemia associated with chronic renal failure: Initial, 50-100 Units/kg IV or SC TIW; maintenance, dose should be individualized to maintain a hemoglobin level of 10.0-12.0 g/dL Treatment of anemia related to therapy with zidovudine: Initial, 100 Units/kg IV or SC TIW for 8 weeks*; maintenance, dose	Safety and efficacy in pediatric patients less than 1 month old have not been established. Treatment of anemia due to the effect of concomitantly administered chemotherapy: Initial, 600 Units/kg IV weekly; maintenance, dose should be individualized to maintain the lowest hemoglobin level sufficient to avoid red blood cell	Multidose vial: 10,000 Units/mL 20,000 Units/mL Single dose vial: 2,000 Units/mL 3,000 Units/mL 4,000 Units/mL 10,000 Units/mL 40,000 Units/mL

Generic Name	Adult Dose	Pediatric Dose	Availability
	should be individualized to maintain desired response Treatment of anemic patients who are at high risk for perioperative blood loss from elective surgery: 300 Units/kg/day SC for 10 days before surgery, on the day of surgery and for 4 days after surgery; alternative dosing schedule is 600 Units/kg SC in once weekly doses at 21, 14 and 7 days before surgery, with a 4th dose on the day of surgery	transfusion Treatment of anemia associated with chronic renal failure: Initial, 50 Units/kg IV or SC TIW; maintenance, dose should be individualized to maintain a hemoglobin level of 10.0-12.0 g/dL	

IV=intravenously, SC=subcutaneously, TIW=three times a week
*For adult patients with serum erythropoietin levels <500 Units/mL receiving a dose of zidovudine ≤4,200 mg/week.

Other Key Facts

Epoetin alfa products are contraindicated in patients with a known hypersensitivity to albumin (human) as they do contain albumin. Darbepoetin alfa comes in two formulations, an albumin solution and a polysorbate solution, which does not contain albumin. Due to the erythropoietin products containing albumin, there is a theoretical risk of transmitting viral diseases and Creutzfeldt-Jakob disease to patients who receive them, although no cases of transmission of either have been identified with albumin.[7-9]

Clinical Guidelines

Table 8. Clinical Guidelines

Clinical Guideline	Recommendations
National Kidney Foundation (NKF) Kidney Disease Outcome Quality Initiative (K/DOQI): **KDOQI Clinical Practice Guidelines and Clinical Practice Recommendations for Anemia in Chronic Kidney Disease (2006)**[17-18]	Recommendations for Anemia in Chronic Kidney Disease (CKD) in Adults • Hemoglobin (Hb) testing should be carried out in all patients with CKD, regardless of stage or cause. • Anemia testing of Hb levels should be measured at least annually. • Diagnosis of anemia should be made and further evaluation should be undertaken when Hb concentrations reach: <13.5 g/dL in adult males and <12.0 g/dL in adult females. • Selection of the Hb target and level at which erythropoiesis-stimulating agent (ESA) therapy is initiated in the individual patient should include consideration of potential benefits (including improvement in quality of life and avoidance of transfusion) and potential harms (including the risk of life threatening adverse events). • In dialysis and nondialysis patients with CKD receiving ESA therapy, the selected Hb target should generally be in the range of 11.0 to 12.0 g/dL. • The frequency of Hb monitoring in patients treated with ESAs should be at least monthly. • The initial ESA dose and ESA dose adjustments should be determined by the patient's Hb level, the target Hb level, the observed rate of increase in Hb level and clinical circumstances. • ESA doses should be decreased, but not necessarily withheld, when a downward adjustment of Hb level is needed. • Scheduled ESA doses that have been missed should be replaced at the earliest possible opportunity. • ESA administration in ESA-dependent patients should continue during

Clinical Guideline	Recommendations
	hospitalization. • Hypertension, vascular access occlusion, inadequate dialysis, history of seizures or compromised nutritional status are not contraindications to ESA therapy. • The route of ESA administration should be determined by the CKD stage, treatment setting, efficacy, safety and class of ESA used. • Convenience favors subcutaneous (SC) administration in non-hemodialysis (HD)-CKD patient and intravenous (IV) administration in HD-CKD patients. • The CKD stage, treatment setting, efficacy considerations, and class of ESA should determine frequency of administration. • Convenience favors less frequent administration, particularly in non-HD-CKD patients. • Iron status tests should be performed every month during initial ESA treatment and at least every 3 months during stable ESA treatment or in patients with HD-CKD not treated with an ESA. • Results of iron status tests, Hb, and ESA dose should be interpreted together to guide iron therapy. • Sufficient iron should be administered to generally maintain the following indices of iron status during ESA treatment: HD-CKD: serum ferritin >200 ng/mL, transferrin saturation (TSAT) >20%, or reticulocyte Hb content (CHr) >29 pg/cell; nondialysis-dependent-CKD (ND-CKD) and peritoneal dialysis-dependent-CKD (PD-CKD): serum ferritin >100 ng/mL and TSAT >20%. • There is insufficient evidence to recommend routine administration of IV iron if serum ferritin level is >500 ng/mL. When ferritin level is >500 ng/mL, decisions regarding IV iron administration should weigh ESA responsiveness, Hb and TSAT level, and the patient's clinical status. • Androgens should not be used as an adjuvant to ESA treatment in anemic patients with CKD. • There is insufficient evidence to recommend the use of L-carnitine or vitamin C (ascorbate) as adjuvants to ESA treatment in the management of anemia in patients with CKD. • Patients with anemia and CKD should undergo evaluation for specific causes of hyporesponse whenever the Hb level is inappropriately low for the ESA dose administered. Such conditions include, but are not limited to: a significant increase in the ESA dose requirement to maintain a certain Hb level or a significant decrease in Hb level at a constant ESA dose or a failure to increase the Hb level to greater than 11.0 g/dL despite an ESA dose equivalent to epoetin alfa greater than 500 IU/kg/wk. • Evaluation for antibody-mediated pure red cell aplasia (PRCA) should be undertaken when a patient receiving ESA therapy for more than 4 weeks develops each of the following: sudden rapid decrease in Hb level at the rate of 0.5 to 1.0 g/dL/wk, *or* requirement of red blood cell transfusions at the rate of approximately 1 to 2 per week, AND normal platelet and white blood cell counts, AND absolute reticulocyte count less than 10,000/µL. <u>Clinical Practice Recommendations for Anemia in CKD in Children</u> • In the pediatric patient, diagnosis of anemia should be made and further evaluation should be undertaken whenever the observed Hb concentration is less than the fifth percentile of normal when adjusted for

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	age and sex. • Selection of the Hb target and selection of the Hb level at which ESA therapy is initiated in the individual pediatric patient should include consideration of potential benefits (including improvement in quality of life, school attendance/ performance, and avoidance of transfusion) and potential harms (including the risk of life-threatening adverse events). • In pediatric dialysis and nondialysis patients with CKD receiving ESA therapy, the selected Hb target should generally be in the range of 11.0 to 12.0 g/dL and should not be greater than 13.0 g/dL. • In the pediatric patient, the route of administration should be determined by the CKD stage, treatment setting, efficacy considerations, the class of ESA used, and the anticipated frequency and pain of administration. • In the pediatric patient, the frequency of administration should be determined by the CKD stage, treatment setting, efficacy considerations, and class of ESA; as well, consideration should be given to the anticipated frequency of, and pain on administration of each agent and their potential effects on the child and family. • Sufficient iron should be administered to maintain the following indices of iron status during ESA treatment: HD-CKD: serum ferritin >100 ng/mL AND TSAT >20%.
European Renal Association/ European Dialysis and Transplantation Association (ERA/EDTA): **European Best Practice Guidelines for the Management of Anaemia in Patients with Chronic Renal Failure (2004)**[33]	• All patients with chronic anemia associated with CKD should be investigated for possible treatment, irrespective of the stage of kidney disease and requirement for renal replacement therapy. • A work-up for a diagnosis of anemia should be considered in patients with CKD when Hb concentration falls below the mean –2 standard deviation (SD) (i.e. <95%) Hb level of the normal population, adjusted for age and sex: <11.5 g/dL in adult female patients, <13.5 g/dL in adult male patients, and <12.0 g/dL in adult male patients aged >70 years. • An initial clinical and laboratory evaluation should be completed prior to considering the commencement of treatment with an ESA in patients with CKD, to evaluate possible causes of anemia superimposed on relative erythropoietin deficiency. • In general, patients with CKD should maintain a target Hb concentration of >11.0 g/dL [hematocrit (Hct) >33%]-or reach this target within 4 months of starting treatment-regardless of age, gender or ethnicity. • ESAs should be given to all patients with CKD with Hb levels consistently (i.e. measured twice at least 2 weeks apart) below 11.0 g/dL (Hct <33%), where all other causes of anemia have been excluded. This applies equally to patients with CKD (stages 1–5) developing anemia, patients with CKD stage 5 treated with HD or PD and transplant patients with chronic renal insufficiency and anemia. • For patients on HD, the IV route may be preferable for comfort and convenience, but the SC route can substantially reduce the dose requirements of ESA. • Epoetin alfa (Eprex®, Erypo®) is not licensed for SC administration in all CKD patients in many European countries (including all member states of the European Union) due to the risk of PRCA. • Darbepoetin alfa can be given either IV or SC without dose adjustments in all CKD patients. In HD patients, darbepoetin alfa may be easier to administer IV, but the SC route is preferable in all other CKD patients. • In patients treated with PD, the intraperitoneal (IP) route of administration is not currently recommended due to the poor bioavailability of ESAs when given by this route.

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	• In HD patients receiving IV epoetin alfa or epoetin beta, the drug should be given three times per week during both correction and maintenance phases. Evidence does not support the use of IV epoetin alfa or epoetin beta once weekly. • During the correction phase, darbepoetin alfa should be given once per week either IV or SC in HD patients, and once per week SC in CKD, PD and transplant patients. During the maintenance phase, darbepoetin alfa can also be given less often (e.g. every 2–4 weeks) either SC or IV in selected patients. • Darbepoetin alfa can be given once every 2 weeks either SC or IV to patients previously given SC epoetin alfa or beta once weekly. • In the correction phase, the starting dose for ESA-naive patients should normally be 20–30% higher than the maintenance dose. • During the correction phase, Hb levels should be monitored once every 2–4 weeks. Initially, the rate of increase in Hb levels should be 1–2 g/dL per month. A change of <1 g/dL in Hb level may indicate the need for a 25% stepwise (up or down) adjustment in the total weekly ESA dose. A rate of increase in Hb level >2 g/dL per month is undesirable and should be adjusted by temporarily withdrawing ESA therapy or by decreasing the total weekly ESA dose by 25–50%. • During the maintenance phase, when Hb levels are stabilized, Hb levels should be monitored every 1–2 months, and perhaps even less frequently in CKD patients not on dialysis. A change of >1 g/dL in Hb level may indicate the need for a 25% stepwise adjustment in the total weekly ESA dose (up or down) and/or dosing frequency according to the type of ESA. • Target blood pressure should be the same as for CKD patients who are not receiving ESA therapy. ESA dose may need to be reduced, especially if there is a rapid increase in Hb concentration. • The function of the vascular access should be monitored in all HD patients to prevent thrombosis. However, treatment with ESAs does not necessitate increased surveillance of the vascular access. • The dialysis schedule should not be altered during ESA therapy as the incidence of potential adverse events such as seizures and headache, loss of dialyzer clearance and hyperkalemia does not significantly increase. There is also no increased need for heparin anticoagulation during HD in patients receiving ESA therapy. • All CKD patients with renal anemia undergoing treatment with an ESA should be given supplementary iron to maintain (or reach) the targets set, regardless of dialysis status. Patients undergoing HD usually have greater iron requirements than those not undergoing HD. • The optimal IV iron dose is 25–150 mg/week for the first 6 months of ESA therapy. • During initiation and titration of ESA therapy, iron status should be checked every 4–6 weeks in patients not receiving IV iron, and every 1–3 months in patients receiving IV iron, until the target Hb concentration is reached. • Dialysis should be optimized to ensure the effective treatment of renal anemia. To maximize the effects of ESA therapy, the eKt/V should be >1.2 in a three times weekly HD program and >1.8 in a weekly PD program. • Treatment with vitamin E may lessen oxidative stress, which is associated with resistance to treatment with ESAs. A single dose of oral

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	vitamin E (1,200 IU) given 6 hours before an HD session, along with intensive IV iron, may protect against oxidative stress-related diseases in the long term. • Correction of impaired vitamin C status can reduce resistance to ESA therapy (hyporesponsiveness) and potentiate the effect of vitamin E. High-dose treatment with IV vitamin C requires monitoring. • Routine folic acid or vitamin B_{12} supplementation of HD patients receiving ESA therapy and an adequate mixed diet is generally not necessary. • A subpopulation of CKD patients (those on maintenance HD) may benefit from carnitine supplementation, but this form of adjuvant therapy with ESAs is not recommended for general or routine use. • Reduced glutathione and other antioxidant treatments may reduce resistance to erythropoietic protein therapy through the reduction of oxidative stress. • Transfusions should not be given unless patients have one or more of the following: symptomatic anemia and/or associated risk factors, acute worsening of anemia due to blood loss or hemolysis, severe resistance to, or hyporesponsiveness to, ESA therapy, e.g. due to the presence of a hematological disease or severe inflammatory systemic disease. • Resistance to ESAs should be suspected when a patient either fails to attain the target Hb concentration while receiving more than 300 IU/kg/week (~20,000 IU/week) of epoetin alfa or 1.5 mg/kg of darbepoetin alfa (~100 mg/week), or has a continued need for such high dosages to maintain the target. • The most common causes of incomplete response to ESAs are iron deficiency, either absolute or functional, and inflammatory disorders. Compliance should also be checked in patients self-administering an ESA. The following conditions may cause apparent resistance to ESA therapy. They should be evaluated and, if reversible, treated: chronic blood loss, hyperparathyroidism/osteitis fibrosa, aluminum toxicity, hemoglobinopathies (e.g. *a*- and b-thalassemias, sickle cell anemia), vitamin deficiencies (e.g. folate or vitamin B12 deficiency), multiple myeloma, myelofibrosis, other malignancies, malnutrition, hemolysis, inadequate dialysis, adverse effects of certain drugs (e.g. cytotoxic and immunosuppressive agents, and angiotensin-converting enzyme [ACE] inhibitors). If the patient has none of these conditions, anemia in ESA-resistant patients should be fully investigated including referral to a hematologist. • PRCA should be strongly suspected if a patient treated with an ESA for $\geq$ 4 weeks has: a sudden, rapid decline in Hb concentration of ~0.5–1 g/dL/week despite ongoing ESA therapy, or requires transfusion of 1–2 units of red blood cells per week to maintain Hb level AND normal platelet and white cell counts AND a reticulocyte count<$10x10^9$/L. Otherwise, look for other causes of resistance to ESA therapy. • If antibody-mediated PRCA is confirmed, all forms of ESA therapy should be stopped. • Iron availability should be assessed by measuring the percentage of hypochromic red blood cells (HRC), the percentage of TSAT or CHr. HRC is the best currently available marker to identify functionally iron-deficient patients who are likely to increase their response to ESAs after supplementary iron therapy.

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National Comprehensive Cancer Network (NCCN): **Cancer- and Chemotherapy Induced Anemia Clinical Practice Guidelines in Oncology (2008)**[34]	Cancer-related Anemia • It is recommended that transfusions be the only appropriate treatment for anemic patients with solid tumors who are not undergoing chemotherapy, as ESAs are not indicated in these patients. Symptomatic Chemotherapy-induced Anemia Not Requiring Immediate Intervention • ESA therapy is considered a treatment option for anemia in patients who are receiving non-curative therapy only. PRBC transfusions may be considered in those patients who are receiving either curative or non-curative therapy. • Those patients who may be considering ESA therapy should discuss the risks and benefits of ESA therapy. Those who do undergo therapy should have their serum iron parameters measured and iron supplementation should be administered as indicated. It is also recommended that these patients receive periodic re-evaluation for symptoms and risk factors for anemia. Asymptomatic Patients Receiving Myelosuppressive Chemotherapy • ESA therapy may be considered in asymptomatic patients receiving non-curative myelosuppressive chemotherapy and who have risk factors for the development of symptomatic anemia requiring transfusion. Those patients considering ESA therapy should be counseled on the risk and benefits. Those who receive ESA therapy should have iron parameters measured to asses for necessity of iron supplementation. Those patients without risk factors should receive periodic re-evaluations for symptoms and risk factors. ESA Therapy: Administration and Response Assessment • Of the two ESAs available, epoetin alfa and darbepoetin alfa, the panel consensus is that either agent can be used. • Initial doses of epoetin alfa recommended for therapy include 150 units/kg SC three times weekly and 40,000 units SC once weekly. • For darbepoetin alfa, recommended dosing schedules include 2.25 µg/kg SC every week or 500 µg every three weeks. Response Assessment and Dose Titration • It is recommended that Hb levels be measured weekly until they stabilize and a dose reduction of 25% to 50% of either ESA product (individualization may be needed) should occur if levels increase by ≥1 g/dL in a 2 week period. If the Hb level increases by <1 g/dL after 4 weeks of epoetin alfa therapy or 6 weeks of darbepoetin alfa therapy, the doses should be titrated up. Epoetin alfa dose should be increased from 150 units/kg three times weekly or 40,000 units weekly to 300 units/kg three times weekly or 60,000 units once weekly, respectively. If darbepoetin is used, the dose should be increased from 2.25 µg/kg once weekly to 4.5 µg/kg once weekly. Iron supplementation may be considered to improve response to ESA therapy. Re-evaluation should be done after 8 to 9 weeks of therapy and ESA therapy should be discontinued in those who have no response (PRBC transfusion should be considered). • ESAs should be discontinued when chemotherapy is complete and anemia has resolved, usually within 6 weeks.

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	Iron Monitoring and Supplementation • Prior to initiating ESA therapy, patients should receive iron studies including serum iron, TIBC, and serum ferritin to rule out absolute iron deficiency, which may respond to oral iron therapy. • After discontinuation of ESA therapy, "functional" iron deficiency often occurs and iron supplementation is usually required. It is recommended that IV iron products be used for repletion in cancer patients with an absolute iron deficiency (ferritin <30 ng/mL, transferrin saturation <15%) or in patients receiving ESAs.
American Society of Hematology/American Society of Clinical Oncology (ASH/ASCO): **Use of epoetin and darbepoetin in patients with cancer: 2007 ASH/ASCO clinical practice guideline update**[35]	• Each patient should be thoroughly assessed (i.e. medications) and other causes of anemia (iron, folate and B12 deficiency) should be ruled out. Consideration should be given to minimize use of ESAs in patients with high risk of thromboembolic events. • Based on current literature comparing the efficacies of epoetin alfa and darbepoetin alfa in patients with chemotherapy-induced anemia, these agents are equivalent with respect to effectiveness and safety. • To increase Hb and decrease transfusions, epoetin alfa or darbepoetin alfa are both recommended as treatment options for patients with chemotherapy-associated anemia and a Hb concentration that is close to or <10.0 g/dL. Red blood cell (RBC) transfusion is also an option depending upon the severity of the anemia or clinical circumstances. • Clinical circumstances (including but not limited to elderly individuals with limited cardiopulmonary reserve, those with underlying coronary artery disease or symptomatic angina, or substantially reduced exercise capacity, energy, or ability to carry out activities of daily living) should be used to determine if epoetin alfa or darbepoetin alfa should be used immediately in those patients whose Hb concentration is <12.0 g/dL but not near 10.0 g/dL, or wait until the Hb levels fall closer to 10.0 g/dL. • Due to clinical data published regarding the increased risk of thromboembolism with epoetin alfa or darbepoetin alfa therapy, risks (i.e. history of thromboses, surgery, and prolonged immobilization/ limited activity) should be evaluated and caution should be used with these products. RBC transfusion is also an option when warranted by clinical conditions. • The Food and Drug Administration (FDA)-approved starting dose of epoetin alfa is 150 U/kg TIW or 40,000 U weekly SC and is 2.25 µg/kg weekly or 500 µg every 3 weeks SC for darbepoetin alfa; escalating dose schedules should follow the FDA-approved labeling. There is a lack of data supporting greater effectiveness with the use of alternative starting doses and different escalating dosing schedules. • ESA therapy should be discontinued in patients who have failed to respond (<1-2 g/dL rise in Hb or no diminution of transfusion requirements) after 6-8 weeks of therapy. These patients should be evaluated for underlying tumor progression, iron deficiency, or other etiologies for anemia. • Epoetin alfa or darbepoetin alfa should be titrated to raise (or near) the Hb concentration to 12 g/dL. It is recommended to reduce the dose when the Hb rise exceeds 1 g/dL in any 2 wk period or exceeds 11 g/dL. Risk of venous thromboembolism should also be considered when determining dose reduction schedules. • The necessity of Epoetin alfa therapy may be decreased by assessing baseline and periodically monitoring iron, TIBC, transferrin saturation, or

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	ferritin levels and instituting iron repletion when indicated, maximizing symptomatic improvement and determining the reason for epoetin alfa failure. There is inadequate evidence to specify the optimal timing, periodicity, or testing regimen for such monitoring. • There is data supporting the use of epoetin alfa or darbepoetin alfa in patients with anemia associated with low-risk myelodysplasia; however, there is a lack of substantial data to support their use in anemic myeloma, non-Hodgkin's lymphoma, or chronic lymphocytic leukemia patients in the absence of concurrent chemotherapy. Recent data supports a stronger recommendation against the use of ESAs to treat anemia associated with malignancy, or the anemia of cancer, among patients with either solid or non-myeloid hematological malignancies who are not receiving concurrent chemotherapy. This recommendation is consistent with the black-box warning that was added to the prescribing information for both epoetin alfa and darbepoetin alfa in March of 2007, as follows: "Use of ESAs increased the risk of death when administered to a target Hb of 12.0 g/dL in patients with active malignant disease receiving neither chemotherapy nor radiation therapy. ESAs are not indicated in this population." • For patients with myeloma, non-Hodgkin's lymphoma, or chronic lymphocytic leukemia, treatment should begin with chemotherapy and/or corticosteroids and their hematological outcomes observed that are achieved solely through tumor reduction before considering epoetin alfa. If a rise in Hb is not observed following chemotherapy, treatment with epoetin alfa or darbepoetin alfa for myeloma, non-Hodgkin's lymphoma, or chronic lymphocytic leukemia patients experiencing chemotherapy-associated anemia should follow the recommendations outlined above. Particular caution should be exercised in the use of epoetin alfa or darbepoetin alfa concomitant with chemotherapeutic agents and diseases where risk of thromboembolic complications is increased. Blood transfusion is also a therapeutic option.
The HIV medicine association of the Infectious Diseases Society of America (IDSA): **Guidelines for the management of chronic kidney disease in HIV-infected patients (2005)**[36]	• All patients at the time of HIV diagnosis should be assessed for existing kidney disease with a screening urine analysis for proteinuria and a calculated estimate of renal function). • Use of recombinant human erythropoietin should be considered in patients with hemoglobin levels 2 g/dL less than the lower limit of normal; the therapeutic hemoglobin target is a hemoglobin level of 11.0–12.0 g/dL. • Recombinant human erythropoietin therapy is an appropriate treatment option for patients with symptomatic mild anemia or moderate anemia (hemoglobin level, ≥2 g/dL below the lower limit of normal).
American Society of Anesthesiologists (ASA) Task Force on Perioperative Blood Transfusion and Adjuvant Therapies. **Practice Guidelines for Perioperative Blood Transfusion and Adjuvant Therapies (2006)**[37]	• Literature supports the efficacy use of erythropoietin agents in reducing the volume of allogeneic blood transfused per patient as well as reducing the number of patients requiring such transfusions in select populations (e.g., renal insufficiency, anemia of chronic disease, refusal of transfusion). • It is recommended that erythropoietin be administered when possible to reduce the need for allogeneic blood in certain selected patient populations (*e.g.*, renal insufficiency, anemia of chronic disease, refusal of transfusion). It is recognized that erythropoietin administration is perceived as being expensive and requires time (in weeks) to induce a significant increase in hemoglobin concentration.

Conclusions

There are currently two erythropoiesis-stimulating agents (ESAs) available in the United States: epoetin alfa (erythropoietin) and darbepoetin alfa (a long-acting form of erythropoietin). Both Epoetin alfa and darbepoetin alfa are approved for the treatment of anemia associated with chronic renal failure, and anemia due to the effect of concomitantly administered chemotherapy in patients with metastatic, non-myeloid malignancies. In addition, epoetin alfa is also approved for the treatment of anemia related to therapy with zidovudine in HIV-infected patients and anemic patients who are at risk for perioperative blood loss from elective, noncardiac, nonvascular surgery to reduce the need for allogeneic blood transfusions.[7-9]

The epoetin alfa and darbepoetin alfa products have similar pharmacological actions, but differ in their half-lives. Due to the additional carbohydrate chain on the darbepoetin alfa molecule, the half-life is prolonged by two- to three-fold allowing it to be dosed less frequently than the epoetin alfa products.[5] For the treatment of anemia associated with chronic renal failure (CRF), the recommended frequency of administration of epoetin alfa is three times weekly while darbepoetin alfa is once weekly.[7-9] Clinical trials comparing the efficacy of these agents for the treatment of anemia associated with chronic renal failure as well as anemia due to the chemotherapy have demonstrated no differences between agents.[20-22] Currently, there are no comparative studies among the agents for the other FDA approved indications. Current practice guidelines for anemia of CRF, such as the National Kidney Foundation (NKF) Kidney Disease Outcome Quality Initiative (K/DOQI), and the American Society of Hematology/American Society of Clinical Oncology (ASH/ASCO) guideline for the use of epoetin alfa and darbepoetin alfa in patients with cancer guidelines do not specify a preferred agent. The K/DOQI guideline states that each of the agents are effective at achieving and maintaining target hemoglobin levels and the ASH/ASCO guideline states that based on available data, these agents should be considered equivalent with respect to effectiveness and safety.[17-18,35] If a patient switches from an epoetin alfa product to darbepoetin alfa, the instructions on dosage conversion (i.e. darbepoetin alfa should be administered once a week if a patient was receiving epoetin alfa 2 to 3 times weekly) are provided in the prescribing information for darbepoetin alfa.[7]

The ESAs are commonly used for the treatment of anemia associated with chronic renal failure to improve quality of life and reduce the need for transfusions. According to the K/DOQI Anemia Guidelines, ESAs are critical in the management of anemia of chronic kidney disease. In 2007, K/DOQI Anemia Guidelines were updated with a new hemoglobin target range of 11.0 to 12.0 g/dL (not to exceed 13.0 g/dL) in dialysis and non-dialysis patients with chronic kidney disease receiving ESA therapy. This update was based on recent safety data published by several randomized controlled trials demonstrating an increase in the risk of adverse cardiovascular events and all-cause mortality in patients receiving ESA therapy with a hemoglobin target of >13.0 g/dL. Ongoing clinical trials are expected to expected to provide more information on the use of ESA and hemoglobin targets.[17-18]

Recommendations

In recognition of the evidence demonstrating the efficacy of the erythropoiesis-stimulating agents (ESAs), it is recommended that no changes be made to the current approval criteria.

Aranesp® (darbepoetin alfa) and Procrit® (epoetin alpha) are preferred on The Office of Vermont Health Access (OVHA) preferred drug list.

Epogen® (epoetin alpha) requires prior authorization with the following approval criteria:

- The diagnosis or indication for the requested medication is anemia.

AND

- The patient has had a documented side effect, allergy, or treatment failure to both Aranesp® and Procrit®.

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